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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
BELYAVSKYI, MICHAIL A

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/06/2003 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/881,721	REISNER, YAIR	
	Examin r	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears n the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9-17 and 21-47* is/are pending in the application.

4a) Of the above claim(s) *22-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7, 9-17, 19-21 and 46-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 3/20/03 (Paper No. 9), is acknowledged.

Claims 1-5, 7, 9-17 and 21-47 are pending.

Claims 22-45 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1-5, 7, 9-17,19-21 and 46-47, drawn to a method of inducing tolerance to transplant and method of transplanting a transplant, comprising a step of conditioning the recipient under sublethal, lethal or supralethal condition and wherein the transplant is a cell are under consideration in the instant application.

In view of the amendment, filed 6/12/02(Paper No. 13), the following rejection remains:

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-5, 7, 9-17, 19-21 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,806,529 in view of Bachar-Lustig E et al. (Blood, 1999, v 94, pp 3212-3221) , or Mobest D et al.(Biotechnology and Bioengineering, 1998, v. 60 pp. 341-347), or Vavrova et al. (Hematol.Cell Ther. 1999, v.41 pp105-112) essentially for the same reasons set forth in the previous Office Action, Paper No: 7, mailed 12/17/02.

Applicant's arguments, filed 3/20/03 (Paper No. 9), have been fully considered, but have not been found convincing.

Applicant asserts that: (i) '529 Patent does not teach that the HPCs are cultured ex-vivo under conditions suitable for inducing or enhancing veto activity, (ii) although culturing condition suitable for inducing or enhancing veto activity are taught by Bachar-Lustig E et al or Mobest D et al. or Vavrova et al., these prior art studies do not describe or suggest the use of expanded HPC culture in transplantation; (iii) in the time period between publication of the '529 patent and filing of the instant application no study contemplated or attempted to combine HPC culturing

methodology with transplantation was done demonstrating that there was no motivation to make the present invention.

Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

In addition, the rejection under 35 USC103 does not set any specific time frame when the attempts to combine the references should be made.

The '529 Patent teaches a method of inducing tolerance to a transplant during bone marrow transplantation comprising administering HPC cells from allogenic donor (see entire document, Abstract in particular) . The '529 Patent also teaches that host patient is conditioned prior to the transplantation of hematopoietic stem cells (HPC) . Conditioning may be carried out under sublethal, lethal or supralethal conditions (see column 3, lines 51-60 in particular). The '529 Patent also teaches that donor and recipient are both humans (see Example 1 in particular). The '529 Patent also teaches that said method enable engraftment of MHC-mismatched transplants (see column 2, lines 36-42 in particular).

The '529 Patent does not teaches that said HPC cells are *ex vivo* culturing under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPC cells and inducing differentiation of said HPC cells into $CD33^+$ myeloid phenotype cells prior to transplantation of the transplant.

Bachar-Lustig E. et al. teach that it is possible to culture HPC cells under growth conditions, suitable for inducing or enhancing veto activity of CD34+ cells by expanding *in vitro* the CD34+ cells and use them for transplantation (see entire document, abstract and page 3220 in particular). The said conditions are the same as to growth conditions disclosed in the instant specification (see Materials and Method in particular). It would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property.

Mobest et al., teach *ex vivo* expansion of human CD34+ hematopoietic progenitor cells under condition suitable for inducing differentiation of said cells into $CD33^+$ myeloid phenotype cells (see entire document, Abstract in particular). Mobest et al., also teach that successful ex vivo culture and amplification of human CD34+ hematopoietic progenitor cells that would differntiate into $CD33^+$ myeloid phenotype cells offers the possibility of additional graft manipulation steps, e.g. depletion or elimination of contaminating tumor cells in Autologous grafts, amplification of bone marrow-repopulating hematopoietic cells, generation of immune effector cells, or genetic manipulation of stem cells (see page 341 in particular). The growth condition taught by Mobest et al. are the same as to growth conditions disclosed in the instant specification (see Materials and Method in particular). It would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property.

Vavrova et al. teach a method of *ex vivo* expansion and differentiation of human HPC cells under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPC cells and inducing differentiation of said HPC cells into $CD33^+$ myeloid phenotype cells (see entire document, Abstract and page 106 in particular). Vavrova et al. teach that *ex vivo* expansion of HPC would benefit studies including accelerated engraftment, reduced risk of infection, smaller stem cell harvest and improved effectiveness of genetically modified stem cells. The growth condition taught by Vavrova et al. are the same as to growth conditions disclosed in the instant specification (see Materials and Method and Table 3 in particular). It would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Bachar-Lustig E et al., or Mobest D et al., or Vavrova et al., to those of The '529 Patent, to obtain a claimed method of inducing tolerance to a transplant or a method of transplanting a transplant from a donor to a recipiet comprising a step of *ex vivo* culturing HPC under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPC cells and inducing differentiation of said HPC cells into $CD33^+$ myeloid phenotype cells prior to transplantation of the transplant.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because successful *ex vivo* culture and amplification of human CD34+ hematopoietic progenitor cells under growth conditions that would stimulated to differentiation of the said cells into $CD33^+$ myeloid phenotype cells prior to transplantation of the transplant offers additional possibility and would be beneficial in accelerated engraftment, reduced risk of infection,

additional graft manipulation steps, e.g. depletion or elimination of contaminating tumor cells in autologous grafts, amplification of bone marrow-repopulating hematopoietic cells, generation of immune effector cells, or genetic manipulation of stem cells as taught by Bachar-Lustig E et al., or Mobest D et al., or Vavrova et al. These *ex vivo* cultured , amplified and differentiated CD34+ hematopoietic progenitor cells can be further used in a method of inducing tolerance to a transplant during bone marrow transplantation taught by the '529 Patent. Since the growth condition taught by Bachar-Lustig E et al., or Mobest D et al., or Vavrova et al., are the same as to growth conditions disclosed in the instant specification it would be obvious to a person of ordinary skill in the art at the time the invention was made that the CD34+ HPC obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPC recited in the instant claims absent a showing of unobvious property.

Claims 46 and 47 are included because it would be conventional and within the skill of the art to identify the optimum culturing conditions suitable for inducing myeloid differentiation of cultured HPSc. In addition, Mobest et al. teach the methodology of analyzing the role of individual components of culturing medium for inducing myeloid differentiation of cultured HPSc (see page 344 in particular). Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The following new ground of rejection is necessitated by the amendment filed 3/20/03 (Paper No. 9)

4. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

5. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Dependent claims 10 recites " wherein said veto activity...". There is insufficient antecedent basis for this limitation in base Claim 1, since base Claim 1 does not recite "veto activity".

6. No claim is allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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Technology Center 1600
May 5, 2003

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